UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/314,698	05/19/99	PERRIN S	14791-501(AR

HM22/0207

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EXAMINER	
EINSMANN,J	
ART UNIT	**PAPER NUMBER**
1655	5

DATE MAILED: 02/07/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/314,698	PERRIN ET AL.	
	Examiner	Art Unit	
	Juliet C. Einsmann	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *19 May 1999 and 28 October 1999* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

14) ☒ Notice of References Cited (PTO-892)
15) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
16) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
17) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
18) ☐ Notice of Informal Patent Application (PTO-152)
19) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-10, 12, and 15-24 are indefinite for failing to recite final process step which meets the preamble. For example, claims 1-10 are drawn to a method for identifying and isolating non-redundant nucleic acid fragments, yet the claims recite a final step of sequencing a fragment. The claims do not set forth the relationship between the sequencing a fragment and the identifying and isolating non-redundant nucleic acid fragments and therefore, it is not clear whether the claims are intended to be drawn to a method for identifying and isolating non-redundant nucleic acid fragments or a method for sequencing a fragment. Amendment of the claims to read e.g. "(e) sequencing a fragment identified in step (d) that was not hybridized or was weakly hybridized to the labeled probes, wherein said fragment represents a non-redundant nucleic acid." would obviate this rejection.

Claims 1-10 are indefinite because step (e) refers to itself ("(e) sequencing a fragment identified in step (e)"). This rejection can be obviated by amending the claims to recite "(e) sequencing a fragment identified in step (d)."

Claims 1-14 and 18-21 are indefinite because of the phrase "weakly hybridized," because the specification does not provide adequate definition for this phrase. The specification, at p. 6, provides a definition of weak hybridization where in the signal to noise ratio is less than 0.5, but then continues on to disclose that when the signal to noise ration is less than 0.5 this typically indicates no significant hybridization, and therefore it is unclear if weakly hybridizes means there is some hybridization or no hybridization. The metes and bounds of these claims are therefore unclear.

Claims 2-9 are indefinite because it is unclear to which "fragment" these claims are further limiting since claim 1 refers to "non-redundant nucleic acid fragments", "a random sample of nucleic acid fragments," and "previously arrayed or sequenced fragments."

Claims 11-24 are indefinite because the phrase "the DNA fragment" in step (e) lacks proper antecedent basis. The claims previously mention DNA fragments, but does not specifically refer to one DNA fragment.

Regarding claims 18-20, the phrase "particularly" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

The phrase "decreased hybridization stringencies" in claims 18-20 is a relative term which renders the claim indefinite. The phrase " decreased hybridization stringencies " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the

invention. It is unclear what the initial standard for hybridization stringency therefore it is not possible for one to determine whether or not hybridization is occurring at decreased stringency.

Claims 18-20 are further indefinite because step (e) is drawn broadly to include identifying the DNA fragment by DNA sequencing, hybridization or other analytic approaches and step (e) conflicts with the narrower step (f) which requires comparing the obtained DNA sequence with other DNA sequences. If one were to determine the identity of a DNA sequence by hybridization or some other analytic approach, one would not have necessarily obtained a DNA sequence and it is unclear how one would then complete instant step (f).

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 15-17 and 22-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Pinkel et al (US Patent 5690894).

Pinkel et al. disclose a method for enrichment and/or isolation of DNA sequences that are unique to a population which comprises the steps of: amplifying random samples of nucleic acid fragments, such as by using Alu or degenerate oligonucleotide primers in a PCR reaction (Col. 16, lines 64-65), immobilizing the amplification products as an array to form a biosensor (Col. 17, lines 7-14), exposing the biosensor to labeled nucleic acid probes from two sources (Col. 15, lines 40-47) wherein the labeled nucleic acids can be derived from genomic samples (Col. 16,

lines 37-40) or from mRNA (Col. 16, lines 44-45), detecting hybridization of nucleic acids from the first and second source (Col. 15, lines 60-65), and then determining the identity of the hybridized molecules using clones which have been previously mapped which is an analytical approach for determining the identity of the nucleic acid fragment (Col. 17, lines 46-54). Pinkel et al. teach that this method can be used to detect sequences which are under-represented in a sample or over-represented in a sample by comparing the strength of the hybridization signals from the two nucleic acid populations (Col. 15, lines 18-23).

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-14 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kayne et al. (WO 9843088) in view of Gress et al (Mammalian Genome 3: 609-612, 1992).

Kayne et al. teach a method for identifying and isolating non-redundant nucleic acid fragments which comprises the steps of: providing a library containing undefined nucleic acid sequences (p. 2, lines 9-10), hybridizing said library to a collection of defined nucleic acid sequences (p. 2, line 8), wherein the defined nucleic acid sequences have been previously sequenced and/or are of known origin (p. 3, line 17-18), recovering non-hybridized nucleic acid sequences (p. 2, lines 10-11), and sequencing the non-hybridized nucleic acid sequences (see abstract and p. 9, lines 9-10). In the method taught by Kayne et al., the collection of defined

nucleic acid sequences is bound to a surface (p.2, line 8), wherein the surface may be an array (p. 5, line 31), and the preferred surface for such and array is glass (p. 6, line 12). The method teaches that the sequences to be hybridized to the array should be labeled to permit detection of the DNA which hybridizes to the immobilized sequences (p. 7, line 16-17).

With respect to claims 2-7, 14, and 17, Kayne et al. teach the library of unknown fragments can include gene or gene fragments, may be a random cDNA library, may be genes from an organ, or may be set of RNAs (p. 6, lines 26-28). With respect to claims 8-9, and step (a) of claims 11-14, Kayne teach that a library may also contain PCR products from genomic libraries (p. 4, line 2). With respect to claim 10, Kayne teaches that the label used can be fluorescence, radioactivity, photoactiviation, biotinylation, energy transfer or the like (p. 7, lines 17-19). With respect to claim 13, in the method of Kayne et al., nucleic acids on a grid are exposed to a library containing undefined nucleic acid sequences, and this library is considered to be a set of pooled labeled probes (p. 2, lines 9-10).

The method of Kayne et al. differs from the claimed method because in the method of Kayne et al. the collection of defined nucleic acid sequences is bound to a surface, and in the claimed method the undefined nucleic acid sequences are bound a microarray. Gress et al. teach a method for hybridization fingerprinting of high-density cDNA-library arrays with cDNA pools in which a random cDNA library is hybridized to a micorarray with the help of a robotic device (p. 609). Gress et al. teach that the spotting cDNAs onto a microarray allows for the screening of thousands of clones at one time, and also provides a method which is adaptable for automated analysis.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kayne et al. so as to have spotted the library of random nucleic acids on the microarray in order to have provided an improved method for isolating and identifying non-redundant nucleic acids since concerning large scale DNA characterization projects Gress et al. state, "As we have shown in our work with genomic ligraries, such large-scale projects can most easily be performed with library arrays spotted at high clone density with a robotic device..." (p. 613).

With respect to claims 11-14 Kayne in view of Gress do not explicitly teach step (f) of the instantly claimed invention, which comprises repeating the hybridization, detection, and identification of the probes which did not hybridize in order to identify additional sequences. However, this step would also have been obvious to a practitioner of ordinary skill in the art for the reasons that follow. Kayne et al. do teach that in some cases it is desired to repeat some steps in the method to control the size and content of the resulting subtraciton library (p. 8, lines 7-9), and they specifically teach that "it is preferred that multiple rounds of hybridization are carried out" (p. 8, line 13). Considering this teaching of Payne et al., it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have repeated any of the steps in the method for the added benefit of increasing the amount of sequences detected. Further, "selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results" (MPEP 2144.04). In the instant case, applicant is simply choosing to repeat already disclosed steps, and this would have been obvious to one of ordinary skill in the art.

Finally, the examiner notes that these claims have different preambles, but substantially the same method steps, and a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. In the case of these claims, the preamble was only directed to the purpose of the process, the steps could stand alone and did not depend on the preamble for completeness, and therefore, the different preambles were not given strong consideration in analysis of the claims (see MPEP 2111.02).

7. Claims 18-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pinkel et al. in view of Maslyn et al.

Pinkel et al. teach a method for discovery of DNA sequences which comprises the steps of: amplifying random samples of nucleic acid fragments, such as by using Alu or degenerate oligonucleotide primers in a PCR reaction (Col. 16, lines 64-65), immobilizing the amplification products as an array to form a biosensor (Col. 17, lines 7-14), hybridizing labeled probes to the biosensor (Col. 15, lines 40-47) wherein the labeled nucleic acids can be derived from genomic samples (Col. 16, lines 37-40) or from mRNA (Col. 16, lines 44-45), detecting hybridization of the labeled probes to the biosensor (Col. 15, lines 60-65), and then determining the identity of the hybridized molecules using clones which have been previously mapped which is an analytical approach for determining the identity of the nucleic acid fragment (Col. 17, lines 46-54). Pinkel et al. teach that this method can be used to detect sequences which are under-represented in a sample or over-represented in a sample by comparing the strength of the

hybridization signals from the two nucleic acid populations (Col. 15, lines 18-23), and Pinkel specifically teaches that some hybridization signals will be stronger than others, and it is a necessary fact that if some hybridization signals are stronger there must also be weaker signals. Stringency is an routinely optimizable parameter and Pinkel teaches that standard techniques for hybridization are to be used (Col. 20, lines 1-2).

Pinkel does not teach a step in which the obtained DNA sequences are compared to other DNA sequences.

Maslyn et al. teach that a "cluster" is a group of clones related to one another by sequence homology (Col. 7, lines 43-44), and that determining a cluster is achieved by comparing the sequence of against a library or database of sequences (Col. 12, lines 12-16).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have included the comparison step of Maslyan et al. in the method taught by Pinkel et al. Maslyn specifically teaches that this is a useful method "to look for homologous, and presumably functionally related sequences in other tissues or samples." This is particularly useful in the context of method of Pinkel et al. since Pinkel et al. expressly compares two different cell types and is interested in the relationship between the cell types (Col. 15).

Conclusion

8. No claims are allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C. Einsmann whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the

organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Juliet C. Einsmann
Examiner
Art Unit 1655

January 28, 2000

JEFFREY FREDMAN
PRIMARY EXAMINER